Viral Etiology of Bronchiolitis Among Pediatric Patients

To the Editors:

We read the article by Heinonen et al[1] regarding the association between transient tachypnea (TTN) of the newborn and the risk of hospitalization due to respiratory syncytial virus bronchiolitis. In their article, the authors stated that TTN diagnosis after birth was associated with an increased risk for respiratory syncytial virus (RSV) hospitalization during the first year of life. In the study group although RSV was not detected, assumptions were made according to previous studies. But etiology of bronchiolitis and other respiratory tract infections could change according to geography and season of the study group.

In a study from Taiwan between January 2009 and March 2011, out of 113 children with bronchiolitis, <2 years of age, RSV was the most common pathogen and was identified in only 43.4% of the cases.[2]

In our study, in which 688 pediatric patients hospitalized with the influenza-like disease during the 2017–2018 were evaluated, 74 patients were influenza-positive (22%), 115 patients were RSV positive (34.3%) and 146 patients were positive for other-agents (43.5%) (unpublished data, 2017–2018). In patients admitting to hospital with a presentation of bronchiolitis or other respiratory tract infections, knowing the causative agent is important in terms of treatment of influenza infection and prevention of complications. And also laboratory tests to detect viral causative agents reduce unnecessary use of antibiotics.

Assumption that >70% of bronchiolitis patients younger than 1 years old were caused by RSV could affect prophylaxis regimens and also future treatment plans of RSV, so it could be better to say that TTN of the newborn is associated with an increased risk of hospitalization due to bronchiolitis (not only due to RSV bronchiolitis).

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Heinonen et al[1] also discussed that gestational age at birth, mode of delivery, gender, birth weight, multiple births, older siblings and maternal smoking, TTN was associated with an increased risk for bronchiolitis hospitalization. These studies defining risk factors for bronchiolitis are very helpful to guide clinicians. Further studies, particularly randomized controlled trials, are warranted in pediatric patients with bronchiolitis to fully elucidate the etiology and to guide therapy.

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REFERENCES

1. Heinonen S, Süvari L, Gissler M, et al. Transient tachypnea of the newborn is associated with an increased risk of hospitalization due to respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J.* 2019;38:419–421.
2. Chen YW, Huang YC, Ho TH, et al. Viral etiology of bronchiolitis among pediatric inpatients in northern Taiwan with emphasis on newly identified respiratory viruses. *J Microbiol Immunol Infect.* 2014;47:116–121.

In Reply: Viral Etiology of Bronchiolitis Among Pediatric Patients

Key words: transient tachypnea of the newborn; respiratory syncytial virus; bronchiolitis; risk factor

In Reply:

We thank Ozkaya-Parlakay et al for their interest in our recently published paper. In our study we analyzed the association between transient tachypnea of the newborn at birth and hospitalization due to respiratory syncytial virus (RSV) bronchiolitis during the first year of life.[1] Previous studies in cell cultures and animal models suggested that RSV may inhibit Na+-driven pulmonary fluid transport.[2,3] As similar pathophysiology is present in infants with transient tachypnea of the newborn, we wanted to study if these two clinical conditions were associated. To have a population as homogeneous as possible, we limited our study to bronchiolitis caused by RSV.

Our study was a population-based registry study that was based on International Classification of Diseases, 10th revision (ICD-10), diagnosis codes at discharge but not on viral detections. As Ozkaya-Parlakay et al highlighted, viral etiology of bronchiolitis varies between studies. Most important factors affecting the viral etiology include age and seasonality of RSV epidemics. In younger children and during seasonal RSV epidemics RSV dominates whereas in older children and outside RSV epidemics other viruses are more common.[4,5] However, in contrary to what Ozkaya-Parlakay et al state, our study was not based on assumptions according to previous studies. ICD-10 includes three codes for bronchiolitis: J21.0 (acute bronchiolitis due to RSV); J21.8 (acute bronchiolitis due to other specified organisms); and J21.9 (acute bronchiolitis, unspecified). In our study we included only children diagnosed with J21.0 (acute bronchiolitis due to RSV). As RSV rapid antigen detection tests have been widely available and routinely used in hospitalized children throughout the study period, we believe that the great majority of children with J21.0 diagnosis have tested positive for RSV and J21.8 and J21.9 codes have been used in RSV-negative children and in children who were not tested.

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REFERENCES

1. Heinonen S, Süvari L, Gissler M, et al. Transient tachypnea of the newborn is associated with an increased risk of hospitalization due to respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J.* 2019;38:419–421.
2. Chen L, Song W, Davis IC, et al. Inhibition of Na+ transport in lung epithelial cells by respiratory syncytial virus infection. *Am J Respir Cell Mol Biol.* 2009;40:588–600.
3. Song W, Wei S, Matalon S. Inhibition of epithelial sodium channels by respiratory syncytial virus in vitro and in vivo. *Ann N Y Acad Sci.* 2010;1203:79–84.
4. García CG, Bhore R, Soriano-Fallas A, et al. Risk factors in children hospitalized with RSV bronchiolitis versus non-RSV bronchiolitis. *Pediatrics.* 2010;126:e1453–e1460.
5. Mansbach JM, Piedra PA, Teach SJ, et al; MARC-30 Investigators. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med.* 2012;166:700–706.

Comment on Transient Tachypnea of the Newborn Is Associated With an Increased Risk of Hospitalization Due to Respiratory Syncytial Virus Bronchiolitis

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TABLE 1. Adjusted ORs and Rates of Hospitalizations Due to RSV Bronchiolitis During the First Year of Life in Children With and Without History of TTN Stratified by Age at the Time of RSV Diagnosis

	0–12 mo	0–6 mo	6–12 mo
RSV bronchiolitis hospitalizations, n (%)	181 (4.4)	138 (3.4)	43 (1.1)
Rate of RSV bronchiolitis hospitalizations in children with TTN diagnosis, n (%)	13 (5.9)	8 (3.7)	5 (2.3)
Rate of RSV bronchiolitis hospitalizations in children without TTN diagnosis, n (%)	168 (4.4)	130 (3.4)	38 (1.0)
Adjusted OR (95% CI)*	1.19 (0.66–2.16)	0.93 (0.44–1.94)	2.13 (0.83–5.50)†

*Logistic regression corrected for gestational age, mode of delivery, gender, birth weight, multiple births, older siblings and maternal smoking.
†Logistic regression corrected only for gestational age, siblings and multiple birth.
CI, confidence interval; ORs, odds ratios.

To the Editors:

We read with interest the article by Heinonen et al[1] in which a relation between transient tachypnea of the newborn (TTN) and the risk of respiratory syncytial virus (RSV) hospitalization within the first year of life was demonstrated. In this population-based study, 2 large national database registries were linked to identify children with TTN and RSV hospitalization based on International Classification of Diseases, 9th revision, codes. Multivariable logistic regression analysis was used in which a significantly increased risk was found for TTN and the occurrence of RSV hospitalization after correction for potentially confounding factors. The authors suggest that both entities may share the underlying pathophysiologic defect in sodium-driven pulmonary fluid transport explaining this association.

Despite their large study population, the usage of registry data has limitations such as the lack of data on RSV viral detection. Furthermore, using International Classification of Diseases codes for diagnosis often results in the underdetection of disease compared with using medical chart data, especially for milder conditions.[2] This could have occurred as well for a temporary, mild condition such as TTN, which is often not the primary cause of hospital admission. In contrast, however, the authors reported an incidence of TTN of 1.57%, which is much higher compared with the incidence of 0.4%–0.6% described for term born infants.[3,4] We speculate that perhaps children with mild infant respiratory distress syndrome were included, because distinguishing between these 2 entities can be difficult.

We seek to validate their results in the RISK study,[5] a prospective birth cohort study in 4072 late preterm infants (32–35 weeks gestational age) of whom 181 (4.4%) children were hospitalized with RSV-confirmed infection during their first year of life. Although preterm born infants have an increased risk of both TTN[3] and RSV hospitalization, we attempted replicating the findings of Heinonen and colleagues in our population. We defined TTN as having received isolated oxygen or low-flow nasal cannula oxygenation therapy or as having received continuous or bilevel positive airway pressure (CPAP/BiPAP) for a maximum duration of 1 day. We excluded patients from our definition if they had received prolonged continuous positive airway pressure, mechanical ventilation, surfactant or a full course of antibiotics, or if they were diagnosed with meconium aspiration syndrome, pneumothorax or pneumonia at birth.

TTN was diagnosed in 222 (5.5%) children in our study, which is comparable to the 4.6%–6.4% incidence shown in late preterm infants in literature.[3] Univariate and adjusted multivariable analyses did not show an association between TTN and RSV hospitalization (Table 1).

We acknowledge that our population differs from the study by Heinonen et al with respect to the risk of respiratory disease.[3] Perhaps the multifactorial increased risk of respiratory disease in prematurely born infants overshadows the individual contribution of epithelial ion transport dysfunction in this population. Even though we could not confirm the results by Heinonen et al in our population of late preterm infants, we are interested to see whether their hypothesis can be investigated further in other prospective birth cohort studies in term born infants.

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REFERENCES

1. Heinonen S, Süvari L, Gissler M, et al. Transient tachypnea of the newborn is associated with an